

General

Guideline Title

Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia.

Bibliographic Source(s)

Oscier D, Dearden C, Erem E, Fegan C, Follows G, Hillmen P, Illidge T, Matutes E, Milligan DW, Pettitt A, Schuh A, Wimperis J. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. London (England): British Society for Haematology; 2012. 64 p. [177 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D, Guidelines Working Group of the UK CLL Forum, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol 2004 May;125(3):294-317.

Recommendations

Major Recommendations

Note from the British Committee for Standards in Haematology (BCSH): This guideline replaces the previous BCSH guideline on chronic lymphocytic leukaemia published in 2004 and should be read in conjunction with the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidance published in 2008.

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Major changes since last guideline:

- The diagnosis of chronic lymphocytic leukaemia (CLL) now requires a minimum clonal B cell lymphocytosis of $>5 \times 10^9/l$.
- Two Phase 3 trials have shown that fludarabine + cyclophosphamide + rituximab (FCR) is superior to fludarabine + cyclophosphamide (FC) in previously untreated patients and to alkylating agent or purine analogue monotherapy in relapsed disease.
- Poor outcome following FC and FCR is strongly associated with a *TP53* abnormality, supporting the screening for *TP53* loss pre-treatment and the use of agents that act through p53 independent mechanisms in these patients

Epidemiology

- In view of the low absolute risk of CLL developing in a family member of a patient with CLL and the absence of clinical benefit associated

with early diagnosis, there is no current indication to screen family members for the presence of a circulating clonal B cell population (unless they are potential allogeneic hematopoietic stem cell [HSC] transplant donors) or for genetic susceptibility (grade B1).

Clinical and Laboratory Evaluation

Investigations

- Patients should be screened for a *TP53* deletion pre-treatment (grade A1).
- Patients receiving intensive chemo- or immunotherapy should be screened for hepatitis B and C infection (grade A1).
- Pre- and post-treatment computed tomography (CT) scanning should be considered for patients treated with more intensive therapies. There is no role for routine surveillance CT scans in asymptomatic patients post treatment (grade C2).

Diagnosis of Lymphomatous Transformation

- The possibility of lymphomatous transformation should be considered in patients with bulky or progressive asymmetric lymphadenopathy, high lactate dehydrogenase (LDH), extranodal lesions and/or unexplained B symptoms (grade A1).

Assessing Prognosis

Early CLL

- Measurement of prognostic biomarkers is not currently recommended for patients with early CLL in whom there is no clinical indication for treatment (grade B2).
- Identifying a *TP53* abnormality in patients with no clinical indication for therapy is not an indication for treatment (grade B1).

Pre-treatment

- Patients should be screened for the presence of a *TP53* abnormality prior to initial and subsequent treatment. Currently *TP53* loss should be assessed by fluorescence in situ hybridisation (FISH). However it is likely that this will be superseded by newer technologies able to detect *TP53* mutations as well (grade B2).
- Measurement of biomarkers other than *TP53* loss is not currently recommended outside clinical trials in patients for whom there is a clinical indication for therapy (grade C2).

Management

Management of Patients with No Immediate Indication for Treatment

- Treatment of early stage disease is not currently indicated (grade A1).

Treatment Options

Initial Treatment of Fit Patients with No TP53 Abnormality

- FCR is recommended as initial therapy for previously untreated fit patients outside clinical trials (grade A1).
- Patients who progress after one cycle of FCR or who have stable disease after two cycles have high risk disease and should be managed accordingly (see "Management of High-risk CLL," below).

Initial Treatment of Unfit Patients with No TP53 Abnormality

- Options for patients unfit for FCR include chlorambucil or bendamustine (grade B1).
- Entry of patients into trials of chlorambucil or bendamustine in combination with anti-CD20 antibodies is strongly encouraged (grade B1).
- Further studies are required to determine the efficacy of dose-reduced fludarabine + cyclophosphamide (FC) or FCR (grade B1).

Management of Relapsed CLL with No TP53 Abnormality

Relapse at Least 2 Years after Fludarabine Combination Chemotherapy or Chemo-immunotherapy

- Patients relapsing at least 2 years after FC, FCR or similar regimens who have not acquired a *TP53* abnormality, remain fit enough for fludarabine-based treatment and in whom there is a clinical indication for treatment, should receive FCR (grade B2).
- Further studies are required to evaluate the role of bendamustine in combination with an anti-CD20 antibody in fit patients with relapsed disease (grade B2).

Relapse after or Refractory to Chlorambucil

- Patients relapsing after chlorambucil can be retreated with chlorambucil (grade B2).
- Entry into trials which include bendamustine or chlorambucil and an anti-CD20 antibody is strongly recommended (grade B2).
- In the absence of a suitable trial, bendamustine + rituximab (BR) should be considered for patients refractory to chlorambucil (grade B2).
- The minority of patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR (grade B2).
- Other options for patients who are refractory to chlorambucil and unable to tolerate myelosuppressive therapy include high dose steroids, alone or in combination with rituximab, and alemtuzumab (grade B2).

Management of High-risk CLL

- The management of high-risk CLL is controversial and poses considerable therapeutic challenges. Accordingly, early input from a centre with a specialist interest in CLL is strongly recommended (grade B1/2).
- Treatment for high-risk CLL should ideally be delivered as part of a clinical trial. Outside of trials, alemtuzumab in combination with pulsed high-dose glucocorticoid is the treatment of choice. Meticulous attention should be paid to antimicrobial prophylaxis and supportive care (grade B1/2).
- The use of alemtuzumab in combination with drugs other than steroids should be confined to clinical trials (grade B1/2).
- Since subcutaneous alemtuzumab injection is associated with comparable efficacy and less toxicity in CLL, this has become the preferred route of administration (grade B1/2).
- Ofatumumab is the treatment of choice for patients with high-risk CLL who fail alemtuzumab. Other options include high-dose or conventional-dose glucocorticoids, lenalidomide, or radiotherapy (grade B1/2).

The Role of Allogeneic Transplantation

- Allogeneic stem-cell transplantation should be considered as consolidation therapy for all fit patients with high-risk CLL and should ideally be performed in the setting of a secure remission. Suitable patients should be discussed with a transplant centre at the earliest opportunity (grade B1).
- There is no consensus on the value of screening potential allograft donors for monoclonal B cell lymphocytosis (MBL). It would seem sensible to exclude donors with early CLL or clinical MBL (grade C2).

Consolidation/Maintenance Therapy

Antibody Therapy

- Currently consolidation and maintenance immunotherapy should only be offered in clinical trials as the clinical benefit versus the risk of morbidity is still uncertain (grade B2).

Autologous Transplantation

- In the absence of an overall survival gain or evidence of improved quality of life, autografting is not recommended as part of standard care in CLL (grade A1).

Management of Lymphomatous Transformation

- The diagnosis of lymphomatous transformation requires histological confirmation.
- Depending on the histological subtype of lymphomatous transformation, patients who are suitable for intensive therapy should receive regimens currently employed for either primary diffuse large B cell lymphoma or Hodgkin's lymphoma (preferably in the context of a clinical trial). Younger patients who achieve a good response are candidates for allogeneic stem cell transplantation (grade B2).

Treatment of Small Lymphocytic Lymphoma

- Small lymphocytic lymphoma (SLL) should be managed in the same manner as CLL (grade B2).

Autoimmune Complications in CLL

- A bone marrow aspirate is usually required to confirm the diagnosis of autoimmune cytopenia (grade B1).
- Autoimmune haemolytic anaemia (AIHA) or immune thrombocytopenic purpura (ITP) should be treated before deciding whether therapy for CLL is needed (grade B1).
- First line therapy is prednisolone (grade B1).

- Second line therapies for patients intolerant of or refractory to steroids include cyclosporine, intravenous immunoglobulin (IgG), thrombopoietin mimetic agents (ITP), low-dose cyclophosphamide, rituximab, alemtuzumab, and splenectomy (grade B1).
- CLL treatment may be initiated to control recurrent or refractory AIHA/ITP. Rituximab-containing regimens are recommended in patients who do not have a *TP53* abnormality (grade B1).
- If AIHA/ITP develops during CLL treatment the same regimen should only be used again in that patient with extreme caution and if no effective alternative is available (grade B1).
- Autoimmune neutropenia usually responds to granulocyte colony-stimulating factor (GCSF) (grade B1).

Supportive Care

- All patients should be assessed for risk factors for infection and for current active infection prior to treatment (grade A1).
- All patients receiving immunosuppressive therapy should be screened for hepatitis B and C infection pre-treatment (grade A1).

Immunoglobulin Replacement Therapy

- Immunoglobulin replacement therapy should be considered as a means of reducing the incidence of bacterial infections in patients with a low serum immunoglobulin G (IgG) level who have experienced a previous major or recurrent minor bacterial infections despite optimal antibacterial prophylaxis (grade B2).
- The goal should be to reduce the incidence of infection and the immunoglobulin dose should be adjusted accordingly (grade B2).
- Patients should be reviewed regularly to evaluate the effectiveness of immunoglobulin replacement therapy and whether there is a continuing need for treatment (grade B2).
- Patients who develop serious and/or recurrent infections despite antimicrobial prophylaxis and immunoglobulin replacement should be managed in conjunction with a microbiologist, infectious diseases specialist, and/or immunologist (grade B2).

Immunisation

- Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B (HIB) is recommended at diagnosis. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S pneumoniae* and HIB antibody levels have fallen (grade B2).
- Annual vaccination against seasonal influenza and novel strains is recommended (grade B2).
- Live vaccines such as polio, herpes zoster, and yellow fever should be avoided (grade B2).
- Vaccinations should be avoided, if possible, 2 weeks prior to, during or up to 6 months after chemo-immunotherapy (grade B2).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1) Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

A treatment algorithm for auto-immune haemolytic anaemia (AIHA)/immune thrombocytopenic purpura (ITP) is provided in the original guideline document.

Scope

Disease/Condition(s)

Chronic lymphocytic leukaemia (CLL)

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Hematology

Internal Medicine

Oncology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia

Target Population

Patients with chronic lymphocytic leukaemia (CLL)

Interventions and Practices Considered

Diagnosis/Evaluation/Screening/Risk Assessment

1. Screening family members for the presence of a circulating clonal B cell population or for genetic susceptibility (considered but not recommended)
2. Screening patients for a *TP53* deletion pre-treatment
3. Screening patients receiving intensive chemo- or immunotherapy for hepatitis B and C infection
4. Pre- and post-treatment computed tomography (CT) scanning
5. Consideration of lymphomatous transformation
6. Measurement of biomarkers other than *TP53* loss (not recommended)

Treatment/Management

1. Initial treatment of fit patients with no *TP53* abnormality
 - Fludarabine + cyclophosphamide + rituximab (FCR)
2. Initial treatment of unfit patients with no *TP53* abnormality
 - Chlorambucil
 - Bendamustine
 - Entry of patients into trials of chlorambucil or bendamustine in combination with anti-CD20 antibodies
 - Dose-reduced fludarabine + cyclophosphamide (FC) or FCR
3. Management of relapsed chronic lymphocytic leukaemia (CLL) with no *TP53* abnormality
 - FCR in patients relapsing at least 2 years after FC, FCR or similar regimens
 - Bendamustine in combination with an anti-CD20 antibody
 - Retreatment with chlorambucil in patients relapsing after chlorambucil
 - Entry into trials which include bendamustine or chlorambucil and an anti-CD20
 - Bendamustine + rituximab (BR) for patients refractory to chlorambucil
 - FCR for patients relapsing after chlorambucil who are fit enough
 - Other options for patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy: high dose steroids, alone or in combination with rituximab, and alemtuzumab
4. Management of high-risk CLL
 - Early input from a centre with a specialist interest in CLL
 - Treatment for high-risk CLL delivered as part of a clinical trial
 - Alemtuzumab in combination with pulsed high-dose glucocorticoid
 - Alemtuzumab in combination with drugs other than steroids (confined to clinical trials only)
 - Use of subcutaneous alemtuzumab
 - Ofatumumab for patients with high-risk CLL who fail alemtuzumab
 - Other options: high-dose or conventional-dose glucocorticoids, lenalidomide, or radiotherapy
5. Allogeneic bone transplant
6. Consolidation/maintenance immunotherapy (confined to clinical trials)
7. Autologous transplantation (not recommended as standard care)
8. Management of lymphomatous transformation
9. Treatment of small lymphocytic lymphoma
10. Management of autoimmune complications
11. Antimicrobial prophylaxis and supportive care
12. Immunoglobulin replacement therapy
13. Immunization, with avoidance of live vaccines

Major Outcomes Considered

- Response to therapy
- Rate and duration of remission
- Disease relapse
- Adverse events (e.g., infection)
- Quality of life

- Survival (including overall, progression-free, and disease-free survival)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Recommendations are based on a review of the literature using Medline/PubMed searches under the heading chronic lymphocytic leukaemia, up to August 2011, and data presented at the American Society of Haematology in 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence,

details of which can be found at <http://www.bcsghguidelines.com> .

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of United Kingdom (UK) based medical experts and patients representatives. The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

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Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis, investigation, and management of chronic lymphocytic leukaemia (CLL)

Potential Harms

- Alemtuzumab plus pulsed methylprednisolone or dexamethasone should be regarded as the induction regimen of choice. This regimen is associated with a significant risk of infection and meticulous attention should be paid to antimicrobial prophylaxis and supportive care. Routine antimicrobial prophylaxis with oral co-trimoxazole, aciclovir, and itraconazole and monitoring for cytomegalovirus (CMV) reactivation is recommended.
- The use of alemtuzumab following initial therapy with fludarabine-based regimens has led to an improved complete response rate, minimal residual disease eradication, and prolonged progression free survival, but the potential for infective complications necessitates careful attention to the timing of consolidation therapy and to antimicrobial prophylaxis and treatment.
- Progressive multifocal leucoencephalopathy (PML) has been reported as a rare complication in patients with chronic B cell lymphoproliferative disorders who have been treated with rituximab. This diagnosis should be considered in chronic lymphocytic leukaemia (CLL) patients who develop progressive confusion, weakness, poor motor coordination, speech or visual changes.
- Chemotherapy, immunotherapy with anti CD20 antibodies or alemtuzumab and transplantation may result in reactivation of hepatitis B and/or C virus infection. All patients with CLL receiving immunosuppressive therapy should be screened for evidence of previous hepatitis B or C infection.

Contraindications

Contraindications

Live vaccines such as polio, herpes zoster and yellow fever should be avoided. Vaccinations should be avoided, if possible, 2 weeks prior to, during or up to 6 months after chemo-immunotherapy.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
- The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia. In all cases individual patient circumstances may dictate an alternative approach.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

Oscier D, Dearden C, Erem E, Fegan C, Follows G, Hillmen P, Illidge T, Matutes E, Milligan DW, Pettitt A, Schuh A, Wimperis J. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. London (England): British Society for Haematology; 2012. 64 p. [177 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2004 May (revised 2012)

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Haemato-oncology Task Force of the British Committee for Standards in Haematology

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

None of the authors have declared a conflict of interest (or other statement as agreed between the writing group and the Task Force Chair).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D, Guidelines Working Group of the UK CLL Forum, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol 2004 May;125(3):294-317.

Guideline Availability

Electronic copies: Available from the [British Committee for Standards in Haematology Web site](#) .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

Suggested topics for audit are available in the [original guideline document](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on September 27, 2006. The information was verified by the guideline developer on October 25, 2006. This summary was updated by ECRI on January 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rituxan (Rituximab). This summary was updated by ECRI Institute on October 8, 2008 following the U.S. Food and Drug Administration advisory on Rituxan (rituximab). This summary was updated by ECRI Institute on August 18, 2009, following the revised FDA advisory on CellCept (mycophenolate mofetil). This NGC summary was updated by ECRI Institute on September 10, 2012. The updated information was verified by the guideline developer on September 11, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab). This summary was updated by ECRI Institute on March 19, 2015 following the U.S. Food and Drug Administration advisory on Treanda (bendamustine hydrochloride).

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